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DAVIS, DEBORAH A	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/986,240
Filing Date: October 19, 2001
Appellant(s): WEIGELT ET AL.

Jack Brennan

For Appellant

EXAMINER'S ANSWER

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-10 and 12 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

This is in response to the appeal brief filed Yabuki et al (1998) J. BIOMOLECULAR NMR, 11:295-396

6,060,603	MOORE	9-1995
WO 97/18471	FESIK ET AL	5-1997

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 4-5, 8-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuki et al (Journal of Biomolecular NMR, 11: 1998) in view of Graham J. Moore (USP#6,060,603).

Yabuki et al teaches a method for stable-isotope labeling of proteins by cell free synthesis. In this method, a technique that utilizes Ras protein samples in which the main chain carbonyl carbons of one amino acid type (AA1) are labeled with ^{13}C carbons and another amino acid type (AA2) is labeled with ^{15}N are evaluated with HNCO-type NMR and 2D1-H-15N NMR (see NMR measurements, pg 299 and pg. 300, Figure 1). The amino acid Ser^{39} (AA2) occurs directly subsequent to Asp^{38} (AA1) as recited in claim 1 (pg. 301, paragraph 1). Yabuki et al evaluates several amino acid labeled pairs by NMR techniques; such as, the amino acids Asp and Ser are labeled in a pair located within the Ras protein (pg. 300, paragraphs 1 and 2). The labeled Ras protein was then

complexed with the binder protein Raf RBD, and evaluated with NMR HNCO spectrum and then compared with the results of the NMR spectrum of labeled amino acid pairs (pg. 301, paragraph 1 and pg 302, Figure 3). Chemical shift differences such as cross peaks of labeled amino acid pairs of the Ras protein were observed, compared, recorded both by itself and complexed with the Raf RBD, indicating interaction between the labeled Ras protein and the Raf protein complexed with the binding protein as recited in claim 1 (pg. 300, last paragraph and pg. 301, first paragraph). The Ras-Raf RBD complex has a molecular mass of about 30 kDa as recited in claim 8 (pg. 300, last paragraph). The reference points out that labeled amino acid pair, Pro-Thr is unique in the Ras protein and was identified by the HNCO experiments as recited in claims 4 and 5 (pg. 300, paragraph 5, lines 17-19). This dual labeling technique can be performed on very large proteins with a molecular mass of about 150 kDa (pg. 296, paragraph 2). Thus, dual labeling and site-directed labeling by cell-free protein synthesis will be useful techniques for analyzing the structures of proteins as recited in claim 12 (pg. 305, last paragraph, last 3 lines).

Yabuki et al does not teach that the potential binder molecule has a molecular mass from 50-1000 Da.

However, Graham J. Moore teaches the use of NMR techniques which are employed to evaluate tertiary structures of biological active ligands that has a molecular weight of < 500 or > 2000 Daltons (col. 3, lines 1-46) and also includes through-bond coupling patterns within a molecule (col. 13, lines 22-50). Preferably, when analyzing by NMR, the ligand should have a molecular weight of less than 3,000 Daltons.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Yabuki et al to include the use of small molecular weight ligands to evaluate tertiary structures of biological active ligands as taught by Graham J. Moore. Further, absent evidence to the contrary, the range recited in the instant claims from 50-1000 Daltons is viewed as mere optimization of the prior art assay.

Claims 2-3 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yabuki et al in view of Graham J. Moore and in further view of Fesik et al (WO97/18471)

The teachings of Yubuki et al and Graham J. Moore are set forth above and differ from the instant claims by not teaching the sphere radius of the labeled amino acid pair, the proximity of an active site within the protein, neither does Yabuki mention the result of the above described method is compared to the result of any other binding or activity assay.

However, Fesik et al teaches a method for identifying ligands which bind to a specific target molecule labeled with radioactive isotopes and said ligand binding is evaluated by NMR. Studies were also performed to compare binding constants of ligands to various biomolecules, determined by the NMR method, such as enzymatic, filter binding and gel shift screening assays (pg. 26, lines 18-24 and pg. 27, lines 1-9). An advantage of using NMR in screening assays is the ability to correlate observed chemical shifts from two-dimensional NMR correlation spectra with other spectra projections of target molecule configuration (pg. 24, lines 1-14).

It would have been obvious to one of ordinary skill in the art to incorporate a comparison method of the various assays as taught by Fesik et al into the method of Yabuki et al in view of Graham J. Moore to compare the binding of ligands to various biomolecules determined by NMR and to also observe chemical shifts from observed by 2-D NMR techniques. With respect to claims 2, 3 and 6, one skilled in the art would recognized that the proximity and spatial orientations of amino acids within a protein can be modified in such a way to get the desired results, especially since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

(11) Response to Argument

Patentability of Group 1, Claims 1, 4-5, 8-10 and 12

1. Applicant's argues that the reference of Yabuki is concerned with investigations of protein structure and the characterization of protein complexes, the skilled artisan would have had no reason to modify the methods of Yabuki to create a method that screens candidate compounds to evaluate their ability to bind to Ras or any other protein. Furthermore, neither Yabuki nor Moore describe a single low molecular weight compound (i.e., having a molecular mass of from 50 to 1000 Da, as is required by the claims) that was known to bind to Ras that the skilled artisan even might have attempted to use in the method of Yabuki in place of Raf to investigate the nature of a Ras-ligand interaction.

This argument is noted but is not found persuasive because the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

There is motivation and suggestion in the Moore reference to modify Yabuki. Yabuki teaches a method for stable-isotope labeling of proteins, which include structural analysis using NMR. The reference of Moore teaches structural analysis of a protein by investigating the tertiary structures of active ligands that has a molecular weight of 500 or 2000 Daltons (Moore, col. 3., lines 1-46), therefore, one of ordinary skill in the art evaluating the two references would agree that Yaubuki and Moore are combinable. Moore also modifies the reference of Yabuki by teaching design mimetics wherein the method screens for agonist and antagonists of ligands (col. 2, lines 66-67 and column 3, line 1). Further, the reference of Moore was relied on for its teaching of analyzing binder molecules or potential binders having a molecular mass from 50 to 1000 Daltons; wherein Moore explains that it is preferred that ligands should have a molecular weight of less than 3,000 Daltons when being analyzed by NMR. Therefore, it is the position of the examiner that the reference of Yabuki in view of Moore is properly combined and is obvious over the instant claims.

2. Applicant argues that the WO 97/18471 reference does not add to the reference of Yabuki and Moore et al because this instant reference teaches a process of identifying compounds with a potential binder versus Yabuki that teaches analyzing structures of proteins. This argument is noted but not found to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Yebuki and Moore have been fully discussed above. WO97/18471 was applied, not to reactivity any problem with Yabuki and Moore as asserted by appellant, but to teach a limitation of appellant's on dependent claims. As such, appellant's argument is not germane to the rejection on appeal.

3. Applicant argues that dependent claim 12 requires that the method of independent claim 1 be used for screening a "compound library" and nothing in Yabuki or Moore, taken alone or in combination suggests applying the dual amino acid-selective labeling method of Yabuki to a "compound library" to identify molecules in the library that bind to a polypeptide or protein of interest.

In response, the office Initially points out that claim 12 is a dependent claim whose patentability stands or falls with claim 1. Otherwise, appellant should have separately grouped this claim from claim 1. Further, Yabuki teaches a method for stable-isotope labeling of proteins, which include structural analysis using NMR. The

reference of Moore modifies the reference of Yabuki by teaching design mimetics wherein the method screens for agonist and antagonists of ligands using NMR screening techniques (col. 2, lines 66-67 and column 3, line 1). Therefore, it is the position of the examiner that Yabuki and Moore are combinable.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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March 11, 2005
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